Priority Date

The Examiner has established a priority date of 06/18/99 for the instantly claimed application, because the application to which priority is claimed does not recite the limitation "except when the target cells are malignant and normal haematopoietic and lymphatic cells". Applicants do not agree with the Examiner's established priority date for the presently claimed invention. However, as the publication date of the art relied upon by the Examiner predates December 12, 1996, further discussion regarding the proper priority date are not warranted.

101 Rejections

Claims 9-11 and 13 were rejected under 35 U.S.C. 101 as being drawn to non-statutory subject matter. Applicants respectfully traverse the rejection to the extent that it is maintained.

The Examiner stated that the use of a method is not a statutory class of invention. Claims 9-11 and 13 were amended to recite a method rather than the use of a method. As such, the claims constitute statutory subject matter. Withdrawal of the rejection is respectfully requested.

Indefiniteness Rejections

Claims 1-4, 6-11, 13, and 14 were rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse the rejection to the extent that it is maintained.

The Examiner stated that claims 1-4, 6-11, and 13-14 were indefinite because claims 1 and 14 recited "each antibody conjugated to each of several types of particles." The Examiner further stated that it was unclear whether each antibody was conjugated to one type of particle or several types of particles. Claims 1 and 14 have been amended to clearly state that an individual antibody is conjugated to one type of particle and different individual antibodies can be conjugated to different particles.

The Examiner stated that claims 1-4, 6-11, and 13-14 were indefinite because claims 1 and 14 recited "0.01 μm-6 μm." The Examiner further asks if this size refers to the antibody conjugate or the particle alone. Claims 1 and 14 have been amended to clearly indicate that the size refers to the particle alone.

The Examiner stated that claims 1-4, 6-11, and 13-14 were indefinite because claims 1-4, 6-8, and 14 recited "characterized". The Examiner further stated that substituting "wherein" for

"characterized" would obviate the rejection. The Claims have been amended to replace "characterized in that" with "wherein".

The Examiner stated that claims 1-4, 6-11, and 13-14 were indefinite because claims 1 and 14 recited "such as". The language "such as animal and human cells" has been deleted from claims 1 and 14, and incorporated into new dependent claims 15 and 16, respectively.

The Examiner stated that claims 1-4, 6-11, and 13-14 were indefinite because claims 1 and 14 recited "a per se known enrichment procedure". The Examiner further stated that it is not clear what type of "per se enrichment" is. The claims have been amended to eliminate "a per se known", leaving the language "an enrichment procedure". Applicants assert that "an enrichment procedure" is clear to one of skill in the art.

The Examiner stated that claims 6 were indefinite because it uses the language "listed in table 1". The Examiner further stated that reciting a Markush group including the antigens of table 1 could obviate the rejection. The claim has been amended to recite a Markush group including the antigens of table 1.

The Examiner stated that claims 6 and 7 are indefinite because claim 7 is dependent on claim 1, which specifically recites that the method is not used with malignant cells. Claim 1 excludes only haematopoetic and lymphatic cells, which are normal or malignant. It does not exclude other types of cells that are malignant. Following this line of reasoning, Applicants respectfully assert that claims 6 and 7 are clear and definite.

The Examiner stated that claim 13 was indefinite because there was no antecedent basis for several terms recited. The terms have been deleted from claim 13.

The Examiner also stated that claim 13 was indefinite for reciting "related" and "associated". Such terms have been deleted from claim 13.

The Examiner stated that claims 1-4, 6-11, and 13-14 were indefinite because claims 1 and 14 recite "the number or of particles". The claims have been amended so that they now recite "the number of particles."

The Examiner stated that claim 14 was indefinite because it was dependent upon canceled claim 5. Claim 14 has been amended such that it no longer depends upon canceled claim 5.

The Examiner stated that claims 9-11 and 13 were confusing for the recitation of the term "Use" of a method. The claims have been amended to recite a method, rather than the use of a method.

Lastly, on page 5 item 13 of the office action, the Examiner suggested minor claim amendments to make the claims more clear. Applicants have amended the claims as suggested by the Examiner.

In view of the above amendment and remarks, Applicants respectfully assert that the instant claims are clear and definite. Withdrawal of the rejection is respectfully requested.

Lack of Antecedence Objection

The Examiner has objected to the specification as failing to provide proper antecedent basis for the claimed subject matter. Applicants respectfully traverse the objection to the extent that it is maintained.

First, the Examiner stated that claims 1 and 14 are drawn to a method and a kit to detect and phenotype target cells by using several types of particles coated with antibodies, wherein each antibody is conjugated to several types of particles. The Examiner further stated that the specification does not disclose a method to detect and phenotype target cells, wherein each one antibody is conjugated to several types of particles. Claims 1 and 14 have been amended to more clearly state that an individual antibody is conjugated with one type of particle. Support for which can be found throughout the specification.

Second, the Examiner stated that claims 1 and 14 are drawn to a method and a kit to detect and phenotype target cells, except when the target cells are malignant and normal haematopoetic and lymphatic cells. The Examiner further stated that the specification only discloses a method for identifying and characterizing pathological cells. Applicants respectfully assert that the specification provides adequate support for the claimed invention. The description discloses the claimed method, with examples of detecting breast cancer cells on pages 4-19. Further, Table 1 lists specific antigens and corresponding antibodies that can be used in the claimed method or kit.

It is well known in the art that the use of specific antibodies depends on the object of the study. Cells have many known antigens expressed on their surface, and the choice of antibody depends on the situation. Thus, a person skilled in the art would know to choose an antibody that

would recognize a known antigen on the target cell of interest. For example, if a person with knowledge in the art was interested in detecting and characterizing a breast cancer cell, he/she would, e.g., use a particle conjugated to an antibody directed to, e.g., C-erbB-2 (HER2, Table 1). The choice of antibody is decided according to the object of the study, and all persons with knowledge in the art will know this and use the most relevant known antibodies.

In view of the above amendment and remarks, Applicants respectfully assert that the specification, along with common knowledge of one skilled in the art, provides support for the instantly claimed invention.

Withdrawal of the objection is respectfully requested.

Lack of Enablement Rejection

Claims 1-4, 6-11, 13 and 14 were rejected under 35 U.S.C. 112, first paragraph, for allegedly lacking enablement.

First, the Examiner rejected claims 1-4, 6-11, 13 and 14 because the specification does not reasonably provide enablement for a method and a kit to detect and phenotype target cells by using several types of particles coated with antibodies, wherein each antibody is conjugated to several types of particles. Applicants respectfully traverse the rejection to the extent that it is maintained. The claims have been amended to more clearly state that an individual antibody is coated with one type of particle and that different individual antibodies can be coated with different types of particles. Support for which can be found throughout the specification. Withdrawal of the rejection is respectfully requested.

Second, the Examiner rejected claims 1-4, 6-11, 13 and 14 because the specification does not reasonably provide enablement for a method to detect and phenotype target cells, except malignant and normal haematopoetic and lymphatic cells. Applicants respectfully traverse the rejection. The Examiner further stated that the specification does not disclose specific antigens, nor corresponding antibodies, for any target cells. Applicants respectfully assert that the specification provides adequate enablement for the claimed invention. The description discloses the claimed method, with examples of detecting breast cancer cells on pages 4-19. Further, Table 1 lists specific antigens and corresponding antibodies that can be used in the claimed method or kit.

It is well known in the art that the use of specific antibodies depends on the object of the study. Cells have many known antigens expressed on their surface, and the choice of antibody depends on the situation. Thus, a person skilled in the art would know to choose an antibody that would recognize a known antigen on a target cell of interest. For example, if a person with knowledge in the art was interested in detecting and characterizing a breast cancer cell, he/she would, e.g., use a particle conjugated to an antibody directed to, e.g., C-erbB-2 (HER2, Table 1). The choice of antibody is decided according to the object of the study, and all persons with knowledge in the art will know this and use the most relevant antibodies. As such relevant antibodies are well known to persons skilled in the art, the specification enables one skilled in the art to make and use the invention commensurate with the scope of the claims. That is, one skilled in the art, armed with the instant specification, can detect and phenotype any target cell, except malignant and normal haematopoetic and lymphatic cells. Withdrawal of the rejection is respectfully requested.

Additionally, the Examiner stated that claim 7 is inoperative because claim 7 is dependent on claim 1, which specifically recites that the method is not used with malignant cells. Claim 1 excludes only haematopoetic and lymphatic cells, which are normal or malignant. It does not exclude other types of cells that are malignant. Thus, claim 7, which is drawn to a method of detecting target cells, wherein the particles used for the method are coated with antibodies directed to tumor associated antigens, is indeed operative.

Obviousness Rejection

Claims 1-4, 6-11, and 13-14 have been rejected under 35 U.S.C. 103(a) as allegedly being obvious over Hajeck et al., U.S. Patent No. 5,340,719, in view of Fostad et al., WO 98/07139, and O'Briant et al., Cancer 68:1272-1278, 1991. Applicants respectfully traverse the rejection.

The presently claimed method is directed to detection and characterization of single cells, on which the expression of relevant antigens can be studied simultaneously. This method is performed such that the type of particle immediately represents information on which receptors are expressed on the cell in question. By detecting and determining the antigen receptors on, for example, metastatic cells, the presently claimed method makes it possible to develop an early and simple plan for therapeutic treatment of metastatic cells. Additionally, that the combination

of two or more antibody-particle complexes could be used together without interfering specificity, strength and sensitivity was not at all predictable, but highly surprising.

Applicants respectfully assert that one of skill in the art would not combine the cited references to arrive at the present invention and that if the references were combined, one would not arrive at the present invention.

The Examiner stated that it would have been obvious to use the method taught by Hajek to screen tumor cells because 1) Hajek teaches that said method of screening target cells using a plurality set of microspheres, each set coated with a different antibody, could be applied to screen tumor cells as well, and 2) there is a heterogeneity of antigenic phenotype within tumors, and even within tumor cell lines, such as in breast cancer cells, as taught by O'Briant. The Examiner further stated that it would have been obvious to use conditions for incubating antibody-coated particles with tumor cells, such as the duration of incubation, temperature, the ratio of particles and tumor cells, and relevant tumor antigens which could be targeted by available antibodies as taught by Fostad, because said parameters are optimal for tumor cells.

Hajek uses a cell population comprising many cells, i.e. bone marrow cells which are coarsely sorted out from large cell populations. The method of Hajek is a screening method not requiring high specificity and sensitivity. In contrast, the present method comprises detecting few target cells in a larger population of non-target cells, and thus is not a screening method, but a detection and characterization of a single cell. Due to the profound difference in the aim of the presently claimed method and that of Hajek, the differences in the methods themselves, as well as the level of specificity required, one of skill in the art could not learn anything from the method of Hajek in arriving at the claimed invention.

Like Hajek, the method of O'Briant lacks the specificity required by the presently claimed invention. Thus, O'Briant does not overcome the deficiencies of Hajek. O'Briant uses particles for unspecified removal of tumor cells, and notably not all tumor cells are removed. O'Briant also discloses the use of drugs in addition to beads, making it impossible to distinguish between the effect of the drug and the effect of the particle. Furthermore, due to the lack of specificity of O'Briant, one of skill in the art would not have drawn a connection between O'Briant and the presently claimed invention. A mere look at the abstract of O'Briant would make one skilled in the art put aside the publication in attempting to arrive at the presently claimed method. In summary, O'Braint does not overcome the deficiencies of Hajek, nor would

one skilled in the art consider combining the teachings of Hajek with O'Braint to arrive at the presently claimed invention.

One of skill in the art would not have combined the teachings of Fodstad with Hajek and O'Braint to arrive at the present invention, nor would they have had a reasonable chance of successfully obtaining the claimed invention if such a combination were made. One would not have used the teachings of Fodstad in arriving at the present invention because the conditions for using paramagnetic beads, disclosed in Fodstad, differs from conditions for using non-paramagnetic beads, as in the presently claimed invention. The conditions are different for using paramagnetic beads and non-paramagnetic beads, because the former contain iron and are also much heavier. Additionally, several types of paramagnetic beads used together will not work because this will give unspecific binding, and high specificity is of course necessary in the presently claimed method. Therefore, it could not be predicted from the teaching in the cited reference that the present method would have been successfully achieved.

In summary, one of skill in the art would not have combined the cited references to arrive at the presently claimed invention, and if they did combine the references, they would have no reasonable expectation of successfully obtaining the presently claimed invention,

Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendment and remarks, Applicants respectfully assert that the claims are in condition for allowance. Notice to that effect is earnestly solicited. If the Examiner has any questions regarding the foregoing, it is respectfully requested that the Examiner call the undersigned.

Respectfully submitted,

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